difference in mortality between the treatment and the control group.

This is a Kaplan-Meier curve again put together by our statistician. It's a little hard to see the six-month survival here but you can see there is really no difference between the treatment and control.

This just shows the implantability of the Attain leads. There was a 92.6 percent success rate of implantability. Again, as the sponsor has outlined, the majority of the cases were related to inability to access the coronary vein and/or inability to obtain distal location.

There was only one generator complication seen in the six-month point. However, during the 12-month point there was an additional generator removed secondary to a partial electrical reset.

I would like to review the coronary sinus trauma just because, again, this is what makes this device very unique is the implantation of that third lead in the coronary sinus. Out of the 579 implant procedures, there were 23 coronary sinus dissections

and 12 coronary vein or coronary sinus perforations. Only six of those were considered a complication requiring intervention. There was a six percent increase of coronary sinus trauma.

This slide just shows the InSync system in Attain LV lead results. The numbers are listed here and the sponsor has already gone through all those numbers.

So as far as the Attain LV lead results, the sponsor did meet their safety endpoints. They did meet their lead performance endpoints. They had adequate electrical performance seen during the study.

The clinical summary, the sponsor did meet their safety endpoints. Again, they did meet their lead performance endpoints, and they did meet their primary effectiveness endpoints.

Thank you.

DR. SWAIN: Great. Thank you very much.

Mitchell, would you like to read the questions the FDA has for the panel?

MR. SHEIN: Sure. These questions parallel very closely with the ones we reviewed for this

morning's session but we will make sure they are of record now.

The first question is the clinical study section of the PMA contains a summary of the adverse events, complications, and observations for the system as a whole, each individual component including the Attain 2187, 2188 lead system reported during clinical investigation.

Part A is: The rate of coronary sinus trauma including CS Dissections and perforations observed in this study with the Attain lead system was 4.1 percent, 24 events in 579 implants. That was just corrected by Dr. Barold. It's the six percent rate.

Please discuss potential safety issues associated with implantation of a lead in the coronary venous system and comment on whether the data in the PMA support the safety of the lead system for the proposed indication.

Part B is: Please discuss the clinical importance of the overall adverse events, complications and observations, and comment on whether the data in the PMA provide reasonable assurance of

the safety of this device system.

Question 2: The primary endpoints of this study were change in NYHA class; Quality of Life under the Minnesota Living with Heart Failure Survey and six-minute hall walk distance.

The secondary effectiveness endpoints were mortality, QRS duration, Peak VO_2 enchocardiographic indices of cardiac function and dimensions, health care utilization and neurohormonal levels.

Question at Part A is: Please discuss the clinical relevance of the effectiveness endpoints for this patient population. Part B, the study was designed with six months of follow-up.

A small percentage of patients underwent functional testing analysis at 12 months and it appears that there may be a diminution of treatment effect at 12 months with the studied parameters. Please discuss whether six-month follow-up is adequate to assess safety and effectiveness in this patient population.

Question 3: The control group saw an improvement in their NYHA classification, QOL score

and six-minute hall walk.

Part A: Please comment on this improvement in the control group. Part B: Please discuss whether the magnitude of the difference between the control and treatment groups is clinically meaningful.

Question 4: Please discuss whether the data in the PMA provide reasonable assurance of effectiveness for this device in the patient population studied.

Question 5: One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize benefits and minimize adverse effects. If you recommend approval of the device, please address the following questions regarding the product labeling.

Part A: Please comment on the operator instructions as to whether they adequately describe how the device should be used to maximize the benefits and minimize adverse events.

Part B: Please provide any other recommendations or comments regarding the labeling of this device you might have.

Question 6: Please identify and discuss the items that you believe should be contained in a physician's training program for this device. For example, please comment on whether training should be required for proper placement of the Attain 2187/2188 lead system.

Question 7: Based on the clinical data provided in the panel pack, do you believe that additional clinical follow-up or post market studies are necessary to evaluate the long-term effects of biventricular pacing on heart failure?

Part A: Please discuss how you would design such a study, including study design, sample size, patient characteristics and potential endpoints.

Part B: Medtronic's proposed indications for use state that this device is indicated for "patients with advanced heart failure who are in NYHA Class III or IV and have a left ventricular ejection fraction ≤ 35 percent and a QRS duration ≥ 130 ms."

Multiple subgroup analyses have been performed. Please comment on the clinical relevance of these analyses and whether this information is appropriate for inclusion in the label or should be the basis for post approval studies or both.

DR. SWAIN: Great. Thank you very much, Mitch. On behalf of the entire committee, I would really like to thank the Medtronic and the FDA for putting together a very cogent package, well organized, and an excellent on-time presentation.

What we'll do now is go around our primary reviewer, Dr. Pina, and we'll start with 15 minutes for our primary reviewers, 10 minutes for each of the other panel members, and keep going around until everyone finishing asking every question that they have. I trust that the questions and the answers will be very succinct this afternoon.

Dr. Pina.

MS. PINA: Thank you, again, to the sponsor for a very eloquent presentation.

I'm trying to hone in on the population here and I'm trying to understand the population better.

I gather that this is a population that did not need defibrillators?

DR. ABRAHAM: Yes. This is Bill Abraham. Correct.

MS. PINA: So anyone who needed a defibrillator for clinical reasons was excluded?

DR. ABRAHAM: Correct.

MS. PINA: There is also a disparity here with a lot of numbers given. I understand the three month and the six month but then in the six-month group, there are a series of patients, I think 37 in one and 41 in the other, that haven't yet reached the six-month endpoint. That's why they are not included in the analysis.

Do you have more data after this on those 3741? Have any of those people reached the six month and are the data concordant?

DR. ABRAHAM: This is Bill Abraham again. Some of those patients since closing this data base for preparation of this PMA have reached their six-month endpoint. I do not know and we'll have to ask if we've looked at that data yet.

MS. PINA: All right, because, again, the numbers are quite, quite different. As we start boiling down, we are getting into smaller numbers.

In talking about the blinding, I think it's great that the blinding early on was done between the EP people and the heart failure people. But when some of these patients came in and got hospitalized as these patients do, how did you blind the hospitalizations? Usually they come in through heart failure and very often have an EKG as they are walking in the door. How did you blind hospitalization?

DR. ABRAHAM: Yes. Bill Abraham again. We again worked very hard to adequately blind this study including going to fairly great lengths in hospitalized patients. For example, when patients were hospitalized, the electrophysiologist reviewed their electrocardiogram or their rhythm strips.

We took that to perhaps what might be considered to even the absurd degree of patients who were in rooms with hardwired monitors putting construction paper over the front of the monitor so that when the heart failure physician made rounds,

they weren't unblinded by having a look at the monitor.

There were in this study, I believe, four or five episodes of documented unblinding. I think to the best of our ability in such a device trial using fairly extreme means to do so the attempt was to maintain this blind throughout the period of follow-up.

MS. PINA: Some of the patients ended up on inotropes. I understand it was a small percentage of them but as a heart failure doc, I would like to know what I'm doing to the cardiogram. Did the EP people pick up the cardiogram and follow it on a daily basis?

DR. ABRAHAM: Again, those were a couple of the instances where patients may have been unblinded but in many instances those patients did remain blinded because of this collaborative effort where the electrophysiologist would be called in to round on the essentially electrophysiological aspects of patient care including electrocardiogram and rhythm monitoring.

MS. PINA: Don't get me wrong. I think it

is very difficult to do that.

DR. ABRAHAM: And I agree with you that it is very difficult and I suspect it was not perfect but I think as best could be in this sort of trial.

MS. PINA: Some of the results that I see here really remind me of, again, beta-blocker results. The ventricles look smaller. The ejection fraction looks a little bit bigger. The quality of life is a little bit better.

40 percent of your patients were not on beta-blockers. Did you stratify any of the improvements on beta-blocker versus no beta-blocker? Again, try to hone in on who needs this, who is going to benefit from it.

DR. ABRAHAM: Absolutely. An analysis has been performed where the major variables assessed were treatment assignment and beta-blocker usage to try to get at that issue.

In fact, there was the treatment effect remained significant. The beta blocker assignment was not a significant impact on improvement. It appeared that patients improved regardless of their beta-

blocker utilization in this study.

MS. PINA: Is there a diminution of the effect or is it as good as the group as a whole?

DR. ABRAHAM: I think it's as good.

Do we have a backup slide?

DR. MANDA: Dr. Pina, my name is Ven Manda. I'm with Medtronic. I'm an employee of Medtronic. We actually control for beta-blocker usage as a covariant in analysis for each of the endpoints and the interaction between that and the dramatization assigned to the patient. Despite those covariants the retreatment was only the covariant that came out significant in predicting a change in each of the primary endpoints.

MS. PINA: Thank you.

In looking at the baseline cardiogram of the population, it looks like the majority of these patients had a left bundle. Yet, the majority of the patients that I see don't classically have a left bundle and it isn't classically a right bundle. I think our electrophysiology colleagues here know that.

Would you say -- first of all, was the

criteria for left bundle a strict criteria for left bundle or are a lot of these just the IVCDs mixed up in here called left bundles?

DR. ABRAHAM: Bill Abraham again. Let me clarify the distribution if intraventricular conduction blocks or abnormalities in these patients. 80 percent had what could be characterized classically as a left-bundle branch block.

Of the 20 percent that did not, 8 percent had a right bundle-branch block and the remaining 12 percent had something else which might have been a nonspecific intraventricular block or bi-fascicular block, a right bundle with one of the left-sided fascicles involved as well.

If the extension of your question then is responsiveness related to type of conduction defect, the answer based on that analysis is no. It seems that the patients with right bundle or non-specific block benefit as well.

MS. PINA: Okay. Going into the complication area, and the complications at the time of implantation, I realize that a lot of this is going

to be dependent on the operator. I'm concerned. I continue to be concerned about the coronary sinus and even getting into the coronary sinus and extending.

I know you're going through the physician education program but I would like to hear a little bit from our EP colleagues. Is this what should be happening at this level or should these complications related to the lead exist at this point? You had some experienced people in this trial and I would expect experienced people to get into the coronary sinus easier.

DR. CURTIS: Anne Curtis. The issues of coronary sinus dissections were picked up early on. There were some modifications made in softener the guide catheter tip and that is some of what helps.

As an electrophysiologist we are experienced in getting into the coronary sinus and I can tell you it's not quite the same thing getting into a patient with severe heart failure as it is into a 21-year-old student who's got Wolff-Parkinson-White syndrome. It tends to be somewhat more difficult to get into the coronary sinus.

That said, it's not impossible. It just takes a little bit more work. There are different ways of handling this and the more you learn the more you can impart to other people.

You can use a deflectable tip catheter that has nothing to do with the system, just a commercially available catheter to get into the coronary science and feed the guide catheter over. That's one way of doing it.

I think no matter what we do there will be some finite number of coronary science dissections and perforations that will be seen because we're using multiple tools here. I think it probably happens some other times during EP procedures and we don't know it because we don't normally inject dye. If you don't inject contrast, you won't see the overwhelming majority of these.

The only way we pick it up sometimes is by the blush when you put in a little bit of dye. Or sometimes by injecting contrast you see a narrowing in the coronary sinus to suggest that there is a hematoma that has come up.

I think there's a small number that we can expect. I think that we will learn tricks and tools of the trade that we can impart to other people. I think you have to have some care and concern when you do this but I think it can be done safely the overwhelming majority of the time.

MS. PINA: One observation that I made of the neurohormonal profile which I find very interesting, there is a difference in baseline BNP level between the treatment and the control group. Bill, how do you explain that?

MR. ABRAHAM: Yes, Bill Abraham again. I think it's just random chance. I mean, when you measure as many baseline parameters as we've had, some may be different. I think in both instances the BNP levels are substantially high and high enough to be consistent with this group of heart failure patients.

MS. PINA: Okay. And then one last point. The FDA has provided us with a table of subgroup analysis that divides the patients up into QRS with amount of six-minute walk distance, quality of life scoring, and ejection fraction. If you look in there,

again I'm trying to find this group that I would recommend this to.

Milton, you or Bill can answer this. Who is that population and do you beta-block them first and then give them the pace or do you do it together?

DR. PACKER: I'm Milton Packer, heart failure specialist and a consultant to Medtronic. Our heart failure group has been involved in the trials for both Medtronic and Guidant, although I was not directly involved in those studies.

I think that probably the best guide as to who would be a candidate for this device is dictated by the inclusion and exclusion criteria. I think we need to be fairly empiric.

The patients who are described here who are Class III/IV patients, ejection fraction less than 35 percent, QRS greater than or equal to 130 on what would be considered these days reasonably optimal therapy of dig, diuretics, ACE inhibitors in pretty much everyone, and beta-blockers as tolerated.

As I understand it, none of the subgroup, none of the baseline characteristics influenced the

magnitude of the treatment effect. Consequently, there is no data dependent basis for distinguishing amongst subgroups in the patient population that was studied. One now has to go back to the original entire patient population as described in the trial.

MS. PINA: Well, in this particular table none of the Class IV patients met the endpoint as described in the protocol. I don't know if you have that.

DR. PACKER: Yes, I do remember seeing this table before and I have it in front of me now. If I understand it correctly, I think those who were involved in doing this analysis should probably explain the analysis.

Maybe it would be appropriate to do that before I comment on the analysis because my personal sense, and perhaps I am incorrect here, is this is simply a list of within subgroup analyses using a nominal p of .05 asking the question whether the p-value for that subgroup is more than or greater than .05.

The problem with doing that -- and I'll just

give you my own view which is fundamentally, I guess, not a statistical point of view, although I guess I occasionally play one on television -- is the fact that none of these subgroups are powered for a POS in .05. One shouldn't hold these subgroups to a success criteria of .05.

The way I would ask the question is to ask whether there is a significant treatment by baseline variable interaction which then asks the question whether the baseline characteristic played, in effect, on the magnitude of the treatment effect. As far as I know, this table does not do that but the FDA statistician should actually address what was done here.

DR. SWAIN: Yes. Who would like to address that? Dr. Gray or Helen?

DR. BAROLD: Actually, I'll go ahead and address that since I put the table in. This is just a table that I put together from the data that Medtronic actually provided us. It is clearly labeled in there that this is definitely underpowered.

It's just to give an overview of what may

have happened to different subgroups in there. They are clearly underpowered. These are arbitrarily chosen endpoints and there are some comments in there to suggest that just to give an overall picture.

DR. SWAIN: Ileana, you want to finish up on this part?

MS. PINA: Just to finish up on this, I do understand that but, again, I'm trying to hone in on populations because otherwise are we putting pacemakers in everybody who is Class III and that would include a huge number of patients.

It seems from this that the patients who are worse, the Class IVs, the ones with the least distance walked, the patients with the widest QRS perhaps don't always benefit.

At least, again, taking all the statistical caveats to the place, it seems that the very sickest patients just don't do as well. Maybe it's getting the patients earlier rather than later.

DR. PACKER: I think that the -- I think in order to reach that conclusion, I would like to personally see statistical evidence for a treatment by

baseline variable interaction.

You see, some of these p-values could be .06 and it would still be no.

MS. PINA: I understand.

DR. PACKER: At least based on the analyses I've seen on a treatment by baseline variable interaction, there are no significant baseline by treatment variable interactions. It would be hard to reach the conclusion that sickest patients do less well.

In fact, the data is strikingly consistent across all subgroups that can be defined based on baseline variables. That kind of consistency is actually pretty comforting and allows one to refer back to the original inclusion/exclusion criteria.

DR. SWAIN: Could we ask Dr. Wittes to chip in on this one right now?

DR. WITTES: Yes. I actually had put down in my own notes a big question mark by this table much for the same reasons I think Dr. Packer is talking about.

It would be very useful if you want us to

address the subgroup questions. You all know that I am very uncomfortable addressing it. If you do, we need to see not just yeses and nos and not just p-values but we need to see estimated effects and confidence limits and that would give a sense of whether there is evidence of some groups where we are not seeing an effect.

My gut feeling in the absence of numbers is that what we're seeing is in the most extreme groups, the Class IV and the worse groups. We know these are the smallest so it would be nice to see the numbers. Does anybody have the numbers here? In the absence of numbers I always assume homogeneity.

DR. SWAIN: Ileana, did you have any other questions while we're looking that up? We'll give them a second here.

Actually, you can just tell us when you have the answer to that. We're going to start from this side and, Mr. Dacey, questions? We'll have 10 minutes apiece for the panel members and then just go back around again. We'll break at about 3:45.

MR. DACEY: Thank you. In order for

everybody to understand where I'm coming from on this, my first exposure after a lot of experience with patient education was serving on the AHCPR clinical guideline panel for CHF. This, of course, was published in '94.

What impresses me is how the body of knowledge of what we were working with then and what I'm seeing now has changed so dramatically, so substantially. I'm sure patients, for the most part, are not aware of it and perhaps don't care. I certainly am aware of it. I'm not easily impressed. I guess I'm hard to impress with patient education and information materials, but I'm impressed.

I was hoping that one of the conditions we could make is a public health issue out of anybody with a pacemaker like this should not be exposed to those boom boxes in the vehicles as they pass by your house but not quite.

I really have no questions outside of the fact that I'm curious about the long-term implications of even a modest improvement in that ejection fraction. If this, in fact, is the case, is this

creating an expectation for patients, especially the noneschemic with a very low ejection fraction? Does this shape up as a promise for patients? That is one question I would like to address.

DR. ABRAHAM: This is Bill Abraham again. Your question in part is general what promises hold for patients like this. Maybe more specific, I think you mentioned ejection fraction and ejection fraction change. Let me first talk about this in more global terms as a clinician.

Not as an investigator but as a clinician who now has had the opportunity to manage a lot of patients with this therapy and participate in this and other trials of resynchronization therapy. I think this holds substantial promise for patients with heart failure.

We talk a lot about endpoints and one of the questions you've been asked is are these appropriate endpoints. Well, these are very appropriate endpoints for the patient with Class III or Class IV heart failure because what those patients want when they walk into the office is to feel better.

They want to be able to walk further, feel better, be more active. In that regard, I think the consistency of this data in improving those sorts of functional endpoints does support the notion that this is a very promising therapy for many patients.

The ejection fraction data is personally interesting to me, and others may want to comment either on the panel or from the group here.

While we have in the heart failure arena desperately stayed away from the use of the term surrogate in trying to describe outcomes, I think many of us who put our hopes in any potential surrogate put it, in effect, in LV function and LV remodeling.

We think that therapies that have a beneficial effect on the heart -- because, of course, the heart is the primary problem in heart failure -- likely have a beneficial effect on the heart failure in general.

It was reassuring to me that at a mechanistic level the changes in LV ejection fraction, the effects on the echo parallel the improvements in functional capacity.

DR. SWAIN: Great. Thank you.

DR. PACKER: Dr. Swain, if I might, I do have the answer.

DR. SWAIN: Succinctly.

DR. PACKER: To the previous question.

DR. SWAIN: Oh, great.

DR. PACKER: To the previous question. I'm going to just read this out as best that I can. There are three primary endpoints. That's all the data that we can deliver at this point in time. For the Minnesota Living with Heart Failure Questionnaire for Class III patients, the improvement in the control group was minus 9.5, in the treatment group minus 18.0.

If you just subtract medians, it's a 9.5 difference. For Class IV in the control group it's minus 7.0. For the treatment group it's minus 30. For a 23 difference let me just emphasize the magnitude of improvement is greater in Class IV than in Class III. The reason it doesn't reach statistical significance in Class IV is because of the small sample size.

Let me just make the same point for six-minute walk. For Class III the control group improvement is plus 12 meters. For the treatment group it's 39.7 meters. That is a treatment effect in Class III of 27.7 meters.

In Class IV the control group improvement is 8 meters. The treatment effect is 62 meters. The Delta attributable to therapy is 54 meters. Again, the same point. The treatment effect in Class IV is larger than in Class III.

The reason for the lack of p-value within Class IV alone is due to the small sample. The same applies to New York Heart Association class. It could very well apply to all the secondary endpoints. I think that provides considerable reassurance.

DR. SWAIN: Thank you.

Mr. Dacey, further questions?

MR. DACEY: No.

DR. SWAIN: Okay. Mr. Morton?

MR. MORTON: No questions now.

DR. SWAIN: Dr. Kaptchuk.

DR. KAPTCHUK: I pass for a while.

DR. SWAIN: Okay. Dr. Aziz. I wore these guys out at lunchtime, I think.

DR. AZIZ: Let me just address something from a surgeon's perspective. You mentioned that there was an improvement in mitral regurgitation. I think it there were some echo sort of values for that. In sort of simplistic terms, did the MR improve from severe to moderate or severe to mild? What was the degree of improvement in most patients?

DR. ABRAHAM: I guess I'm trying to equate the change in mitral regurgitant jet area to the typical qualitative way that we look at this.

I would say that on average if one categorizes as qualitatively as mild, moderate, or severe, that improvement seen would be about one to two qualitative categories, so from severe to mild or from moderate to maybe a trivial amount.

Again, on inspection of these echocardiograms that is not unusual. It's also not surprising because, remember, one of the things you do is you improve paradoxical septal motion which is likely one underlying mechanism for the improvement of

mitral regurgitation.

DR. AZIZ: Does that go fairly quickly? In mean, in a matter of weeks?

DR. ABRAHAM: That effect seems to occur pretty quickly, although I don't have any data to share with you today on time course of effect in this study. In previous studies smaller mechanistic studies you see acute effects just by turning the therapy on. There may be, and I stress the term may be, a progressive effect as well.

DR. AZIZ: I mean, does it occur before the endiostolic volume decreases in size giving the different mechanisms?

DR. ABRAHAM: Yes. Some of the benefit occurs just with improvement of the paradoxical septal motion just with turning the device on.

DR. AZIZ: Approaching it from a different point of view, surgically when you try to improve injection fraction, not that I really believe in it, like using cardiomyoplasty, even though there is an peri-operatively mortality of maybe 10 to 20, maybe 16 percent, within a few months a number of people die.

Not from pump dysfunction but from arrhythmias.

Now, again, this device doesn't have a mechanism for -- it doesn't behave like an ICD. If you look at the results both in the control group long term and also in your treatment groups, a number of patients died from sudden death. Again, this falls into the inotropic sort of mechanism. You feel better and your VO_2 max improves and all that sort of stuff. But they do have arrhythmias.

This morning I think folks have presented data which had a device that did actually prevent sudden death. Do you think that is a failing in the device or is that a bad question to ask?

DR. ABRAHAM: No. Bill Abraham again. I do not. I think that there really are two therapies that have been discussed today. One is cardiac resynchronization therapy and the other is defibrillation.

I think at the present time we have very clear indications for which patients should receive a defibrillator. It is possible that in the future those indications will expand as studies such as Scott

Heff and others which are ongoing become available in the future.

At this point in time, and again it's very careful to come back to the point that was made earlier, the patients enrolled in this study did not have defibrillator indications. Yes, some patients who have no defibrillator indications and have heart failure will die suddenly. We just can't predict which ones.

I think the incidents of sudden cardiac death in the trial was to me reassuringly low. It was not different between the two groups. More patients died, as you would expect, from progressive pump dysfunction. I don't think there is a concern. I think the data looks as we would expect it to.

DR. AZIZ: I believe one of the contraindications is pulmonary hypertension for putting this device in. Is that right? Is there a level of PA pressures that you consider high? Obviously that is a moving target in some of these patients.

DR. ABRAHAM: It's actually not a

contraindication but was an exclusion criteria to study. Like many heart failure trials, we excluded patients that had severe really limiting primary pulmonary disease which might be intrinsic lung disease and/or limiting pulmonary hypertension. Not because of any true technical concern about efficacy but because it's one of the ways that you just try to develop a more homogenous population for study.

DR. SWAIN: Okay. Dr. Wittes.

DR. WITTES: Just a few questions. First of all, I really want to thank you all for keeping the numerators and denominators straight. It was very -- it was so nice to know what were patients, what were events. It makes it much simpler.

Couple of very quick questions. The group of patients who didn't have the six-month follow-up and so, therefore, were not included in our panel pack, would they consecutive -- let me tell you why I'm worried about it.

Sometimes when you close a database you are missing not just a consecutive group but the group that is the most difficult. For the endpoints is the

most difficult and the data. The question is were they consecutive?

MR. JOHNSON: Jim Johnson. I work for Medtronic. We identified a follow-up closure date. That date was used as -- what we did was said what follow-ups had to be in by that date to minimize the bias. Everyone of those patients who we identified had follow-ups close as of that date. If the follow-ups weren't in yet, we went and made every effort to get them in before we closed the database for analysis.

DR. WITTES: You said every effort. How many did you not get?

MR. JOHNSON: Well, those -- actually when we -- those three -- the top part didn't get to their six-month follow-up because the window that closed was not the six-month follow-up. It was those nine who the six-month follow-up had closed but we didn't get the information for those so it was just nine.

DR. WITTES: Okay. Thank you.

The other question is this. I'm totally convinced -- I shouldn't say totally but I'm convinced

that the treatment is efficacious. I think you have shown us all three endpoints in a very clear way. I don't know how to take the data and estimate from it the degree of effect partly because of the deaths and the fact that those people who died by necessity don't have a measure.

Did you do any kind of sensitivity analysis to ask -- to impute values for them or to look at what would have happened if they were included under various methods and what did you find?

MR. JOHNSON: Again, my first response -- Jim Johnson, Medtronic. My first response is sensitivity analysis. We actually analyze our endpoints twice for the FDA. We submitted the original PMA and then we had to do an update and our results were consistent. There I look at that as somewhat of a sensitivity.

DR. WITTES: That's a different question.

MR. JOHNSON: Right. However, I did do what you suggest and take those patients who had -- not those who were still at risk but those who had died and we weren't going to get anything else from them

and carried their last observation forward and the results were consistent. I can pull them up as we are speaking but they are pretty much the same.

DR. WITTES: I don't need to see it. I just think that as you're -- what I worry about always is reporting effect sizes. There is a tendency to inflate the effect size because they eliminate some of the missing values. I just urge whoever is putting together the label to make sure that doesn't occur.

MR. JOHNSON: The purpose of including the clinical composite was to address that issue. The whole idea of the clinical composite is that it's not fair to characterize someone as better if they are dead because you can get into all sorts of strange circumstances if you don't worry about that.

In fact, the sponsor proactively worried about that. The clinical composite is, in fact, defined in order to address that issue. The effects on clinical composite are not only highly significant but clinically unusually large for treatment effect for heart failure.

DR. WITTES: I appreciate that. I'm just

worried about only reporting the others and not mentioning the clinical composite.

Okay. One more little thing if I have it here. No, that's it. Thank you.

DR. SWAIN: Dr. Krucoff.

DR. KRUCOFF: I don't usually take issue with Dr. Swain about anything but I actually think we weren't put to sleep at lunch. I think the reason we can be quiet is because you guys have done an awful lot of our work for us.

I also want to thank everybody involved from the presentation to your knowledge of your data eloquence of the presentation and also to the FDA team, this panel pack and this presentation. It didn't quite leave me speechless but close enough to be almost asleep. There are a couple --

DR. SWAIN: Dr. Haigney, next question.

DR. KRUCOFF: Actually, I have just a couple of interest issues around the presentation itself. This is an intention-to-treat analysis. I'm a big fan of that. I just want to make sure I understand where potential treatment failure might exist within the

analysis.

Obviously if the lead can't be positioned stably and those numbers to me were readily available, are there any other modalities that led to the cessation of treatment in the treatment group or the administration of treatment in the control group that aren't just the result of mechanical issues with the device.

DR. ABRAHAM: Bill Abraham again. Yes, remember in the trial that patients could be crossed over to active therapy if they developed a bradycardia pacing indication. That was felt to be the ethnically correct thing to do.

DR. KRUCOFF: I'm sorry to interrupt but I just want to make sure I'm hearing what you're saying. That was biventricular therapy if somebody got a pacemaker?

DR. ABRAHAM: Correct. Because, remember, there is a common output to both leads and both leads are in place so by virtue of that they get biventricular pacing if they are turned on.

Crossover for worsening heart failure,

however, was excluded or discouraged by the protocol. There were seven patients who were unable to maintain their treatment assignment. They were included based on the intention-to-treat analysis.

The reasons were that four of these patients developed a brady pacing indication. While a crossover for worsening heart failure was discouraged, it wasn't absolutely prohibited. There were three patients who crossed over for worsening heart failure.

A total of seven patients that crossed over. I don't believe that there were any instances that went the other direction. Is that true? Correct. No patients went from therapy on to therapy off.

DR. KRUCOFF: Thank you. Another couple of logistical questions if patients who are actually to have this treatment eventuate in our routine practice.

I take it that the long-term surveillance of this instrument permanently implanted in a human is essentially like pacemaker surveillance in general. Are there any unusual demands on the patient or unique elements to the surveillance of these things?

DR. HAYES: David Hayes. Since this is the

first time I've spoken, I'm a cardiologist in the Mayo Clinic in Rochester. I serve in an advisory capacity and I have research agreements with Medtronic, Guidant, and ELA. I have stock in Medtronic, Guidant, and St. Jude.

No, there really isn't. The patients need to have the same sort of things followed with any permanent pacemaker thresholds. We look at the memory to find out how much they are pacing and sensing to assure that they are getting therapy delivered as we did in this trial to ensure that there is ventricular pacing.

The only difference is this is handled in conjunction with their heart failure follow-up so that if there are issues with heart failure follow-up, we want to make absolutely certain that the pacemaker is functioning normally.

In terms of device surveillance, long-term follow-up, battery management, replacement, no differences.

DR. KRUCOFF: Thank you. And if an ICD became necessary, it would be a separate instrument

with separate attachments and you would leave this in place? Is that the speculated management strategy?

DR. HAYES: David Hayes again. In fact, I'm not sure if in this study there have been people upgraded. I know at least one patient in the study had a separate device implanted but the approach in general would be to place another right ventricular defibrillating lead and then reconnect that newly placed lead with the already placed coronary sinus lead and right atrial lead into a device, if such a device is available, that gives you both biventricular stimulation and defibrillation.

DR. KRUCOFF: Okay, but that's theoretical?

DR. HAYES: Theoretically. Otherwise you plant a separate device on the opposite side.

DR. KRUCOFF: Okay. The last question. This actually had to do with the discussion we're going to have about labeling. What is to me very important to the clarity of your instrument's effects in this study was the very rigorous way that the stability of their medical regimen was required prior to entering into the trial.

What concerns me a little bit there is as we go out into the real universe of application, how much are we going to be able to emulate that in real practice.

I think we have discussed earlier today a lot of reasons to be concerned about when these patients are not stably identified as being quite ill or on stable medical therapy how many devices get implanted. In your application the whole indication for the device is symptomatic relief and quality of life. These are not patients who have some other indication for a pacemaker.

My concern, and I think Ileana was getting at this before, how can we define that? Do you really think in your own, or in the company's proposed labeling, just to call this Class III or IV heart failure is sufficient for the real universe of application. Should we amplify that someway?

DR. PACKER: If I might, Milton Packer, the requirement for stability here was driven in large part by the attempt to minimize to the degree possible a placebo response.

Very, very common technique in trials looking at clinical status endpoints to have a period of stability in order to make sure that there isn't a lot of variability pre-randomization to minimize the degree of variability post-randomization in the control group.

The panel needs to determine to what degree those stability criteria not only allowed a treatment effect to become apparent, but also allowed the safety profile to be what it was. Clearly this is the patient population studied so that one could depending on your judgement. You could insert the word stable Class III/IV because these were stable Class III/IV patients. I think that would be a reasonable description of the patient population. Now, I'm reflecting personal judgement, not the judgement of the sponsor.

DR. KRUCOFF: That's actually what I'm asking. I'm asking it of the clinical individuals who have been so involved with this.

DR. SWAIN: I think we'll have Dr. Haigney and then the break.

DR. HAIGNEY: Okay. Two quick questions. 50 percent of the patients in the study had ischemic cardiomyopathies, 50 percent noneschemic. Did you see a difference in effect in those two groups of pacing?

DR. ABRAHAM: Bill Abraham again. Did not. Both patient populations improved.

DR. HAIGNEY: And you had a small number of right-bundle branch blocks and I know it's going to be hard to say much about such a small number but your labeling doesn't specify left bundle versus right bundle. Do you feel as though there was a benefit in those right bundles?

DR. ABRAHAM: Bill Abraham again. I think similar to the earlier discussion on Class III/IV heart failure, the directional changes support efficacy regardless of the type of bundle-branch block.

DR. HAIGNEY: One last comment. What is Medtronic's plan for controlling this lead once, say, you get the approval? Many of my electrophysiological colleagues are known for using devices off label and, in fact, going out and using them without perhaps

meeting all the regulatory requirements. Will you insist that they graduate from your training program before they can actually get their hands on the lead?

DR. STANTON: Marshall Stanton. We and Curtis went over what we think is an excellent training program and that is the program that we would recommend for people that are going to implant.

DR. SWAIN: Is that recommend or insist on?

DR. STANTON: I think we would recommend that. We would certainly put everybody through that that we were giving the lead to, yes.

DR. SWAIN: Okay. So you won't provide the lead to anyone who hasn't gone through your training system?

DR. STANTON: Yes.

DR. SWAIN: Thank you.

DR. HAIGNEY: Thank you. That answers my question.

DR. SWAIN: Okay. We're going to break until about two minutes to 4:00.

(Whereupon, at 3:42 p.m. off the record until 3:58 p.m.)

DR. SWAIN: Dr. Laskey will have the next questions.

Okay. Dr. Laskey.

DR. LASKEY: Well, the advantage of being on this side of the table is you wind up with nothing to say or very little to say other than things complementary.

First of all, bravo. It's a well-done study and extremely well presented. Very lucid. I only wish that my colleagues in interventional cardiology could work as well together as you've demonstrated that you brought your disciplines together.

Very quickly, the OPCs that we saw in here for standards for success, those are internally generated. Is that your database in-house or is that just world literature?

DR. CURTIS: No. Anne Curtis. The performance criteria that were set were based on the InSync study that was done outside the United States so we had that preliminary data and that was how we set the criteria for this study.

DR. LASKEY: Great. And the CS trauma

issue, do you just take what you get when you get in there or are you targeting oblate vein or great cardiac vein or inferior vein? I mean, is this why maybe there is a blip here and you're just trying to get somewhere and it's just technically difficult to do? Does it matter? Should you be pacing from A versus B?

DR. HAYES: David Hayes. I don't think we really know the answer to that yet. Some of the early data would suggest the pacing from the mid-lateral wall is the best and that is generally where we try to go first. We may just be limited anatomically to what we can do.

Other times surprisingly you might end up in a milacardiac vein which then takes a turn back up from the apex so you actually end up laterally and serve the same purpose.

In the end you have to make sure that the lead is in a position that is stable both mechanically and electrically. If that's in the mid-lateral wall, that seems to be the best. I have no doubt that you continue to learn how to manipulate the leads better

with time but the bottom line is mechanical and electrical stability.

DR. LASKEY: That's obviously important for training. Let's not be greedy and take what you get.

Just one final point to make sure I understand the magnitude of the effect here. There clearly is an effect and you've demonstrated that consistently. I'm looking through the percentage of patients, of course the patients who experienced improvements.

For example, in the control group 38 percent improved in NYHA versus the 68 percent. 44 percent in the QOL score versus 57. Can you make a ratio of this or just subtract to get a feel for the magnitude of the placebo effect here?

In other words, do I take -- for example, of the six-minute hall walk, 45 percent of the treatment group experienced an improvement versus 27 percent in the control group. Half of your treatment effect is essentially placebo?

DR. PACKER: If I might. There is probably a relatively large potentially unlimited way of

displaying all of these data. Probably the best way is not to define arbitrary cutoffs and to determine what percentage of patients in each group exceed that arbitrary cutoff because one would be faced with a situation of then having to argue for why that cutoff was a good cutoff.

Probably the best thing to do is to the extent it's possible to look at these variables as continuous variables because that's what they are, and to look at the magnitude of the treatment effect corrected for placebo as a continuous variable.

Based on that, the magnitude of the treatment effects here looked at as continuous variables to the extent that you can. Some of the variable are categorical by nature. But to the extent that you can look at them as continuous variables, they can fair very favorably to other drugs that we use for the treatment of heart failure that are considered to produce an improvement in clinical status.

DR. LASKEY: Thank you. One final question about the echo data even though it's not terribly

relevant to the results.

The EF change, can that be attributed just to the improvement in contraction of the septum with biventricular pacing and have nothing to do with synchronization? It's just better septal contraction?

DR. ABRAHAM: Yes. Bill Abraham. Because the studies were done in the assigned treatment mode; that is, patients who were randomized to resynchronization didn't have echos with the device turned off. That is a possibility.

I think the strongest data suggesting that there's an effect beyond just resynchronizing the ventricle are the changes in LV mass. Again, I don't want to overstate this. It's a secondary endpoint and the numbers are smaller because, again, the data from the core lab is incomplete.

DR. LASKEY: I would agree with that but I desperately wanted to see a change in cardiac output and that wasn't there. That is the one thing we would like to see.

Again, congratulations.

DR. SWAIN: Dr. Domanski.

DR. DOMANSKI: I have no questions.

DR. SWAIN: All my questions were asked except one. The question is how many sites had greater than 15 patients enrolled out of these 500 and whatever? I'm sure that answer is right there.

DR. HAYES: David Hayes. Ten centers had greater than or equal to 15 implants.

DR. SWAIN: Okay. So it's really a 10-center multi-institutional trial for all practical purposes. Thank you.

We'll go around again for questions. Mr. Dacey? Mr. Morton? Mr. Kaptchuk?

DR. KAPTCHUK: I had a question about the climate of the physicians of the trial. I was struck by the fact that everybody got their device turned on at the end of the six-month period. That seems to indicate that everyone was confident that this device was going to have a successful outcome of the providers in the trial. Is that right?

I mean, I would normally think you wouldn't be able to tell after the first 10 or 15 patients if there was a beneficial effect but the physicians were

confident even if they had taken a patient that --

DR. ABRAHAM: Bill Abraham. I actually think that it is attributable more to the hopefulness of patients than to the confidence of physicians. In fact, many of us at the outset approached this therapy and I think it is reflected in the design of the study with skepticism about resynchronization therapy. We certainly were not sold at the outsold. I think it was more the patients who had already had a six-month investment in this study wanted to try the therapy.

DR. KAPTCHUK: So patients were unmasked at six months and you said, "Do you want to have the machine on or not?"

DR. ABRAHAM: Correct.

DR. PACKER: Milton Packer. We have had examples in the history of clinical trials in heart failure where patients and physicians have insisted on putting their patients at the end of trial on open-label therapy for drugs that were known and established to be ineffective and dangerous. We are a very strange group.

DR. SWAIN: Dr. Aziz.

DR. AZIZ: Nothing.

DR. SWAIN: Dr. Wittes.

DR. WITTES: No.

DR. SWAIN: Dr. Krucoff.

DR. KRUCOFF: I just have actually one process question and then one question. Can we assume as we go to vote today that the data sets that are incomplete will be completed and reviewed, i.e., the patients who are not yet at their six-month follow-up point and the nine patients who are a little more challenging get follow-up in the core laboratory data? Is that a safe assumption?

MR. DILLARD: Jim Dillard, FDA. I think it's a very safe assumption. I think, until we get all the data in we wouldn't call this completely closed. The second piece to that that I think is important is that labeling changes over time.

It is certainly important to have a complete clinical data set appropriately placed in the labeling so that you as the clinicians get the best view of what a clinical trial tells us. I think that would be important for that reason alone to complete the study.

DR. KRUCOFF: I just have two last quick questions. One, since it's very clear that the benefits that were measured are functional and/or subjective and that mortality is not indicated or touted as a benefit, at the end of the day one thing that occurs to me that is not exactly in the Minnesota questionnaire is was this worth it.

Did you actually just ask the patients was it worth having my procedure and permanently implantable device and surveillance system put in? Was it worth it?

DR. ABRAHAM: Bill Abraham. We did not do that in a systematic way. If you will accept anecdote having enrolled about 50 patients into the trial, we had none that expressed regrets.

DR. KRUCOFF: Okay. I guess my last question that I can't resist just for fun, Milton, the degree of benefit that you all have indicated functionally on top of, as you pointed out, fairly substantial medical therapy might raise some issues in planning future clinical trials with new drugs for heart failure.

Is this going to be a mandatory component of the standard arm? This is a fairly substantial effect relative to new drugs on top of three-drug therapy.

DR. PACKER: Milton Packer. One of the challenges we have in designing any future heart failure trials is that we have to accept the concept of established therapy as background.

We don't do what might be called placebo control trials where the placebo group gets nothing. We do placebo control trials where both groups get what is considered optimal therapy. Over time what is considered optimal therapy changes and hopefully in an enhanced direction.

The way we design clinical trials is that we rely on the judgement of the investigator. We generally tend to require therapies that change survival and allow therapies that allow clinical studies. There is a mandate for life prolonging treatment and there is an option to use symptom reducing treatment.

Subsequent therapy should this device be approved would be on top of this device and the

randomization process should device patients with this device equally into a placebo or treatment group in any subsequent evaluation of a new treatment.

DR. KRUCOFF: So I can't quite yet tell O'Connor he's got to learn something about devices?

DR. SWAIN: Good point. Dr. Haigney.

DR. HAIGNEY: I have no questions.

DR. SWAIN: Dr. Pina.

MS. PINA: I would urge the investigators and the company to continue to look for the echo data because at the end of the day we do count bodies in this population. As we know, and we said it this morning, functional capacity is a surrogate that doesn't always imply survival benefits.

I would like to see some reverse remodeling in the ventricle which is what I think we are inferring with the change in left ventricular endodiastolic diameter mass, etc. The number of echos are really incomplete.

In particular, in the treatment group in some areas there's a lot less in the treatment group. In some measurements there's a lot less in the control

group which I think is going to change the means of the data considerably.

I would really urge that the rest of that data be brought in and that mortality be at least considered in long-term follow-up. We talked about 12-month follow-up here earlier this morning. I think that is a minimum that we would like to see.

DR. ABRAHAM: Bill Abraham. May I mention that we will certainly do that. I may have mentioned during the presentation that the compliance with these follow-up assessments was extremely high, 98 percent in the InSync study.

That means that we do have all of these echos. They just haven't all been read by the core lab yet. You can rest assured that they will be publicly presented and submitted for peer review. We certainly hope to learn a lot more from them than we have to date.

DR. SWAIN: Thank you. Dr. Laskey.

DR. LASKEY: No.

DR. SWAIN: Dr. Domanski.

DR. DOMANSKI: No questions.

DR. SWAIN: What we need to do now is look at the questions that the FDA has asked. The first question is regarding safety. Mitch will have part A up on that. The question is does anyone on the panel have a question about lead safety or system safety, device safety? Okay, no questions.

Then the second part, B part, is to discuss the clinical importance of the overall adverse events and observations and does the data provide reasonable assurance of the safety. I assume the answer is yes to that from the panel? Okay.

Question No. 2 looks at primary endpoints. I believe we've gone over this once today so far, but the relevance of the effectiveness endpoints. Do we agree that they were relevant? Does anyone disagree with that? Okay.

And then whether a six-month follow-up --

DR. DOMANSKI: I'm going to say they are relevant but soft endpoints but appropriate to the enterprise that we're engaged in.

DR. SWAIN: Okay. Six-month follow-up. That is the question that's going to come up. Is it

adequate to assess safety and effectiveness? Does anyone feel it is not adequate, although we would love long-term data.

DR. KRUCOFF: I guess I would have to give voice to that, Julia. I do think that these are functional endpoints and I do think that more sustained follow-up both from mortality and just to understand what we're doing with these folks is going to be very important.

DR. SWAIN: I think as cardiac surgeons we recognize that you need a five-year follow-up to tell the difference between cardiac surgery and angioplasty so certainly these devices are the same thing. A little ding to the cardiologists here.

DR. WITTES: But once you cross over you can't get that information.

DR. SWAIN: Exactly. Exactly. I think we're talking about what we would like to see for effectiveness totally versus what we're dealing with today in this PMA.

MS. PINA: I think we would also like to see the opposite. I would like to see who are the

patients that actually deteriorate at 12 months and whom the therapy does benefit because that's a very targeted population that may, in fact, end up going to transplantation, for example.

DR. SWAIN: I think probably since the FDA at one time went from three months to six months that these comments are relevant to the FDA in the future in heart failure studies.

Question No. 3, looking at the control group improvement. Does anyone want to make any further comments about improvement in the control group? Okay. The B part meaning are the magnitude of differences between the control and treatment group clinically meaningful because of this improvement in the control? Does anyone feel they are not meaningful? Okay.

DR. WITTES: It's not that I don't feel it's meaningful but I do want to reiterate what I said before. I think it's going to be a challenge to try to quantify what the effect is and I think it's one of the things we need to do.

DR. SWAIN: Okay. Thank you.

MR. DILLARD: Jim Dillard. Just perhaps an additional question and maybe this can get handled under the labeling piece. If you could give us any guidance about how to handle the issue of the magnitude and/or the difference for the control group and how we should factor that in to labeling I think would be quite helpful to us, too.

I don't know if anybody has any comments on that because I think the fact that there was such a dramatic change in the control group is something that U.S. clinicians are probably going to want to read about. Maybe not the ones that are here today but those who might use the therapy in the future.

MS. PINA: It's really difficult to settle them on what you should see, for example, in a six-minute walk test because a lot of the literature of six-minute walk has been based on pharmacologic therapy. It's not been consistent and therapies that have improved survival don't always improve the six-minute walk as we've learned with the beta-blockers.

I think if you go back into the SOLVE database where you've got mostly Class II and III

perhaps not as sick as this population, you'll have a sense of what, for example, an ACE inhibitor can do.

But it is so heterogeneous and it is so based on so many other things, I don't think you can pinpoint. I'm surprised they even gave a limit of what they saw as a significant improvement because I would have a hard time doing that.

Same with the quality of life. The Minnesota Living with Heart Failure Questionnaire was really designed more for Class II and III patients, not for that sick population and we are currently looking at other instruments that maybe hone in on that population a bit more. It's going to be really hard to pinpoint a level of difference that would be meaningful. I don't know what would be meaningful for this patient population.

Mitch.

DR. KRUCOFF: I think, Jim, that a very strong key to that, too, is that the more stably or the more clearly we identify a stable patient population commensurate with those enrolled here, the less likely we are to see even more just natural

history or placebo or nontherapy related changes in these tough measures.

To me the one place we can connect to that, and I think this will be a labeling thing, is how do we really convey the careful way the patients were enrolled in the study to the whole universe of clinical use in the labeling.

DR. SWAIN: Excellent. No. 4, sort of the heart of the matter, do we think that the PMA has provided reasonable assurance of effectiveness for this device in the population study? Does anyone disagree with that?

Okay. Then labeling. Several questions about that, indications for patients and all that. I had a couple comments about labeling. I think on page 14 of the patient manual that you need to explain the coronary sinus. It sort of says in the heart and out of the heart but the coronary sinus is different than most pacers so I think there needs to be a civilian explanation of coronary sinus lead.

Then on page 112 it talks about not approaching too closely various things. I think it

needs to be defined a little better about what too closely is. I imagine a protective spouse, you know, keeping five miles away from a telephone line or a microwave or whatever. I think there needs to be some reasonable distance based on electrical engineering properties.

Also, there is a large section about electrocardary. Try not to use it but if you use it, do this and this. I think there needs to be a point in that labeling about if you do use it, what do you need to do to check that you haven't screwed up the device. That's the one thing missing on that.

In the physician's manual it says patients may require close monitoring for the first few months. No where is that mentioned in the patient book. For whatever reason the statement is that the first few months require careful monitoring, that will need to be reflected in the patient book.

Anybody else have any labeling comments, especially in answer to the two questions that we've been asked about operator instructions about our EP?

MS. PINA: In the patient manual I want to

reiterate having to explain to the patients that coronary sinus lead not only needs to be in writing but the picture that you have in there shows this little star coming around the lateral wall so the depiction has to be a bit clearer because I think even if you write it out in lay language, a picture is worth a thousand words.

I think that some mention has to be in there that there may be some difficulty in assessing the coronary sinus which may limit implantation success. I don't think you have to put in there that it may be operator dependent but I think the patient needs to know that they may not be able to get the device in place if that lead cannot be implanted successfully.

Of course, there could be perforations, etc. Although most of them are not problematic and don't lead to any complications. Are there any technical comments on operator instructions that need to be changed?

DR. HAIGNEY: I thought perhaps a little more detail in the technical manual for positioning the lead. Again, a picture is worth a thousand words.

I thought some details were missing.

DR. SWAIN: Okay. Training programs. I would like to --

DR. KRUCOFF: I just want to stay with the indication labeling right up front that I think in fairness to the data, which are very clear that it should be indicated -- I don't want to wordsmith this right now.

You guys can do that but I would suggest that it be something along the lines that this is indicated in patients with chronic Class III to IV congestive heart failure refractory to stable medical therapy. I also think that right up front it should be indicated that this is for symptomatic relief in congestive heart failure and not sort of give the impression that this is a cure or reversal.

DR. SWAIN: Should that be stated there is no evidence of prolongation of life. It is symptomatic?

DR. KRUCOFF: I'm sure that will come out in the data presentation. I think it's important right up front to not simply let this be imputed as a

licensed device to cure heart failure. The way it stands right now it says it's for heart failure.

I think it is commensurate with the data presented that what this device clearly does is palliate or relieve symptoms or improve functional status or something like that, but that it's not survival kind of benefit.

MS. PINA: I think that is an excellent suggestion. I think if we say who remain Class III/IV in spite of optimal medical therapy which includes the drugs that were specifically put on there so that somebody who has never been on a beta-blocker and whose ACE inhibitors aren't maximized just gets given a lead and then the rest of the medical therapy gets forgotten.

DR. SWAIN: Dr. Packer.

DR. PACKER: Milton Packer. I would like to underscore that as well from a pure clinical point of view. I think the concept of stable background medication may be viewed by some physicians as being inconsistent with the word advanced.

To get rid of the word advanced and state

clearly what these patients were because some people -- some physicians think advanced means end-stage on inotropes. I'm just trying to be sensitive to what the biases may be in the field.

I think the wording that you suggested accurately describes the patient population described and will give people insight as to who, in fact, was enrolled in the trial.

DR. SWAIN: Yes.

DR. LASKEY: Can I open up a bit of a can of worms on that? Again, I'm very sensitive to this issue as an interventionalist. You are sent patients with a certain set of data derived from the referring physician who feels X and wants you to do Y.

In practice, these patients will be referred to an EP doc who wields a catheter or to a heart failure doc or from a heart failure doc and says this patient now needs this. I see this as very analogous to blow a balloon up in this narrowing.

DR. SWAIN: Good point.

DR. LASKEY: How do you see this unfolding? And what are the implications for instructions for

use?

DR. HAYES: David Hayes. I'll respond to the first part. I think that it's going to depend a great deal on the institute in the communities and some of these patients will come through. The majority I don't think will be coming directly to the electrophysiologist but will be referred either by the heart failure specialist.

We all know that many of these patients are not being cared for by a heart failure specialist but being cared for by their primary physician. That's been an issue -- the heart failure specialist can speak to this better than I can. This has been an issue in general about how to get those appropriate patients to the heart failure specialist.

From our standpoint of implanting, at least I'll speak for my institution, we would certainly require that somebody before we would consider putting that device in -- and we do the same thing, for example, for hypertrophic cardiomyopathy -- that whatever the other disease state is, that the expert in that area has seen the patient and that, indeed,

they have met the stable medical therapy that has just been described.

I think that from an educational standpoint this is going to require an educational effort directed at not primarily electrophysiologists and heart failure specialists but at the people where most of these patients reside, and that is with the primary care givers and internists.

There will have to be an educational attempt there as to when to refer and the implanting physicians are going to have to learn how to say either they are on stable therapy or, "I don't know and I need the help of somebody who does."

DR. ABRAHAM: Yes. Bill Abraham. I'm actually an optimist here because I think the marketing effort that will need to occur to get these patients from primary care physician to general cardiologist or heart failure specialist to electrophysiologist will actually help improve background therapy for these patients.

I think we have seen that analogy with the introduction of beta-blockers to heart failure therapy

because during the time in which beta-blockers have been introduced and marketed, we have also seen an increase in the utilization of ACE inhibitors for the treatment of heart failure because the marketing message has been your patient should be on an ACE inhibitor before you start a beta-blocker.

I think the message here will be that your patient should be on optimal standard medical therapy including drugs such as ACE inhibitors and beta-blockers before resynchronization therapy. Again, as an optimist, I think this may have a net overall beneficial effect on the treatment of heart failure because of that.

MS. PINA: I do think that a portion of the education has got to go to the community electrophysiologist so that, as Dr. Hayes has well said, they are not tempted to put the device in without having someone take a look at the patient from a medical therapy standpoint and make sure that they are well medicated. I can just see this happening. I fear it's happening.

DR. SWAIN: I think we're hoping that the

marketing is not done on bus stop signs to patients which has happened with some of the drugs.

Okay. The next question is about physician's training program. I actually want to compliment the company in not having an animal model. If you don't know how to put this in a coronary sinus in a heart failure patient, you're not going to learn in an afternoon with a pig. If you know how to do it, you're not going to learn in an afternoon with a pig. I think we don't need animals to learn these techniques, I don't believe.

Does anybody have any other comments about the training program like they think we need animal trials? Okay.

DR. KRUCOFF: I'm sorry. My assumption in the silence here is that this program will be mandatory in order to have these devices appear on the shelves of a hospital's program. Is that the right assumption?

DR. STANTON: Marshall Stanton. Yes.

DR. SWAIN: We captured that on tape previously. If he wouldn't have asked, I would have.

And the final question is regarding to additional clinical follow-up. For people new on the panel, those are requirements for a post-marketing study which are difficult, expensive, difficult for the FDA to monitor, but are necessary when we have questions about safety or effectiveness. With that caveat, is there anyone who would propose that we need other than the usual?

Jim, do you want to explain the usual follow-up of all devices that are approved?

MR. DILLARD: Jim Dillard. I don't know if there is a usual. I think it really depends on the products. I would echo just what you said, Dr. Swain. Just that if there are issues that the panel and/or FDA feel are not fully understood at the time of approvability, and we think that there might be either a specific issue that we should target or something that is lingering from the clinical trial, then many times we look at it in the post-market period and it becomes a post-approval requirement to study that issue in the post-approval period.

Now, there is a difference between a post-

approval study and post-market surveillance which, I think, occurs on a fairly regular basis. Especially for permanent implants and especially for pacemakers when you're talking about tracking of the products and understanding where the products actually are going. There is a fairly extensive program, I think, with most pacemakers to date.

I think really what we're asking for here is there anything that jumps out at you from this particular clinical trial that you think we really need to cover in a post-approval period, or would something like general post-market surveillance as well as tracking suffice?

Does anyone think there is a hole in the study that needs to be plugged by a post-market study?

DR. KRUCOFF: I don't know that I would represent it as a hole. I would suggest with respect to the complexity of the physiology and mechanics of heart failure and the novelty of this particular mechanical intervention, that ongoing surveillance of the patients who are in this and part of this cohort would be important.

I really feel torn because the data and the presentation, everything would lead me towards approval of this device. I would love to leave that clean without conditions. But I have great respect for this disease and for its ability to throw us curveballs if we're not meticulous. With all due respect, I think the post-market surveillance alone, I don't think we have the tools or the organization to find out what we need to know. I would suggest --

DR. SWAIN: Well, there's two issues here. One is as scientists I'm sure that we all could help you design all kinds of studies to do that we would love to see. The other is do we want to require that the FDA formally require a study. We'll have a motion on that. I think there may be some disagreement about that.

Mike.

DR. DOMANSKI: Yes. I think if you're going to require people to collect data, there ought to be some focused question that you're asking, though. I don't think it ought to be just, "I sort of feel uneasy about the whole thing because it's brand new

and let's make them collect a lot of data." I think it's complicated, expensive, and unless it's a little more focused -- unless it's focused it's not very useful.

DR. KRUCOFF: I would definitely focus on mortality and on one of the endpoints that were used as the primary endpoints in the study. One of the qualitative or functional endpoints over a longer term, one and even three-year follow-up.

DR. DOMANSKI: But I wonder, and I'm not sure about the answer to this. In fact, you all can probably answer this question. Now that this study is out there, the thing is completely unblinded and anybody can do anything with that cohort of patients, I can't imagine that cohort of patients yielding meaningful mortality data. Maybe I'm wrong. What do you think?

DR. PACKER: Milton Packer. At the present time all the patients, as has been mentioned, that were in the study have the device turned on in six months and they continue to be followed for death and for major events like hospitalization.

One still can with some value, perhaps not a tremendous amount of value, continue to analyze those patients according to their original treatment assignment. At 12 months that might be interesting because the difference at 12 months between the patients assigned to control and as patients assigned to treatment would be six months difference in the duration of resynchronization.

One group will have been resynchronization for 12 months. One group will have been resynchronization for six months. That is sort of interesting. As one goes further, the two groups become more and more similar so that at three years the difference in duration of resynchronization may be so little that one wonders what the comparison would be about.

My sense is at 12 months the data re likely to be interesting. Not definitive but interesting. As one goes further out, the actual fact that all the treatment and all the patients got the treatment turned on at six months makes longer and longer term follow-up a little bit harder to interpret. At 12

months I think that there is something interpretable.

DR. DOMANSKI: You know, if there was a difference in mortality, hopefully in favor of the treatment group and it probably will be, that would be interesting. I guess we're negative and I don't think I could draw the conclusion if there wasn't a mortality benefit with people on treatment for that long.

Off treatment for six months and on for six months, no difference from the people on for 12. I'm not sure what I would walk away with.

DR. PACKER: I'm not certain that this cohort will provide any meaningful data on mortality except for whatever trends one can look at in the data. I'm more interested in the 12 versus six-month comparison of maybe combined endpoints like death and hospitalization and IV use of heart failure medication.

Mike, I'm not suggesting that this is a perfect solution but it's something that can be gleaned from the existing trial.

DR. DOMANSKI: I'm just trying to avoid

having us -- I mean, obviously you're going to follow these people and you're going to right some favors and stuff like that. I guess what I'm trying to do is avoid an unfocused data dredge mandated by the FDA for no good reason.

MR. DILLARD: Me too.

DR. SWAIN: Okay. Are there any other questions or comments by either the FDA reviewers or the sponsor?

DR. HAIGNEY: I just want to say something. I'm a newcomer to the committee and I'm still not entirely clear about the distinction between the post-market survey versus the study. I think this lead needs to be followed. I think we need to know what the performance of the lead is years out and how many dislodged, are there late perforations. I just don't know what the usual practice is.

MR. DILLARD: Well, and without going on a long-winded discussion, maybe the Medtronic folks want to maybe give just a real quick update about what your expectation would be not only on this cohort but in follow-up by way of any sort of post-marketing effort

that you might have because that might help rather than giving sort of a hypothetical but how we use these tools.

DR. STANTON: Marshall Stanton. First, I think you may be aware you probably get mailings from us twice a year where we do extensive post-market follow-up on all of our devices and all of our leads. Certainly these leads would be included in that follow-up so you'll have long-term performance on those leads.

DR. SWAIN: Thank you. Are there not two other trials out there looking at mortality with CRT? I think what we're going to hear about mortality and prospective mortality trials but I think there are enough data here that still need to be collected that we're going to find out specifically the echo data which I think would be very meaningful if it's going in the same direction.

I agree with Milton that it's sort of an intention to treat basis to look at the 12-month survival. You've got the patients and I think that six months may not make a lot of difference. Let's

say the curve split apart early. It may be important.

DR. ABRAHAM: Bill Abraham. I think there is enough -- first of all, you are correct. There are two trials ongoing, large-scale trials looking at morbidity and mortality. Secondly, I think the level of interest among the investigative community regarding CRT is now adequately high to essentially assure that all of these other studies and follow-up and issues that you've all described are going to be evaluated because that's what we do. We'll be looking at this data and writing papers and following patients for long-term.

DR. SWAIN: I think this panel has to make the decision of whether you want it to be a formal government survey which implies a whole lot of things.

Ms. Moynahan has to read the voting requirements again.

MS. MOYNAHAN: The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990 allows the FDA to obtain a recommendation from an expert advisory panel on designated medical device Pre-Market

Approval applications that are filed with the agency.

The PMA must stand on its own merit and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information. Safety is defined in the Act as a reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions on intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use as conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows:

(1) Approval if there are no conditions attached.

(2) Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education, labeling changes, or further analysis of

existing data. Prior to voting all of the conditions should be discussed by the panel.

(3) Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. SWAIN: Thank you. Do we have a motion? Dr. Pina.

MS. PINA: We do. I move for approval with the conditions that we have spoken about before, that the rest of the data be collected and not just in a surveillance mode but actually followed up closely that we hear about the mortality at one end and the suggestions given by the panel for modifications of the patient and physician education be put into motion.

DR. SWAIN: A second by Mitch. You're proposing a formal post-market study conducted by the FDA?

MS. PINA: Yes.

DR. SWAIN: Okay. So the motion is on the table and seconded with approval with conditions as stated. If you think that either it shouldn't be approved, non-approval, or that it should be approved without a formal market study, then you should vote no.

MS. MOYNAHAN: What we should probably do is take the motion to be approvable with conditions and then we'll take each condition separately and vote on them separately.

DR. SWAIN: Okay. So it will be a motion for approval. Then if that is approved, then we will have motions for conditions.

MR. DILLARD: Can I suggest a process that I think might work? If Dr. Pina could go through each one of her conditions and we'll lay them out and we can vote on each one of them. You can also call to see if there are any other additional conditions that

would be added. Then at the end you'll want to take all of those conditions and put them with the motion and try to vote on it with its entirety.

DR. SWAIN: Okay. We'll do the reverse order. So the conditions are the acquiring of the data on those 37 and 41 patients in each group that have not been entered into the six-month database. No. 2, completion of the echocardiography data with assessment of all the measurements that have been specified as secondary objectives in the protocol.

Mortality assessment with an intention to treat analysis at 12 months. And the modifications to the patient education booklet which have been specified here and the physician training that have been suggested by the panel.

Okay. So there are four conditions. Acquire the remainder of the six-month data, complete the echo data to the six-month point, look at mortality on intention to treat at 12 months, and modify the labeling that we have discussed.

Mike Domanski.

DR. DOMANSKI: Can we discuss these?

DR. SWAIN: Yes. Or if anyone wants any other conditions that we'll end up voting on individually.

DR. DOMANSKI: I certainly agree with three of those. I don't think it makes sense to mandate, however, the 12-month mortality follow-up. I understand that they may write a paper about it but since it's the government mandating it, I think that is a mistake because really the data are going to be hard to interpret if they are the same.

I mean, I understand if they are different than some interpretation but I don't think that is important data. I don't think that is sufficiently important information, particularly given the fact we have other trials that are going to come in with randomized discussion of exactly the same subjects. I would not mandate that one. I would speak against that.

DR. SWAIN: Yes, Dr. Wittes.

DR. WITTES: I have to run but I agree with Mike completely. The other three conditions make sense to me and this one I just feel is going to be

much too difficult and not worth the government's mandating it.

DR. SWAIN: Morton.

MR. MORTON: Clarification. Is the requirement for the six-month follow-up on the remaining patients? As I understand, the PMA approval could continue on without that follow-up.

MR. DILLARD: Jim Dillard. I think working that into your motion, I think what you're saying is the data as you currently see it today would be approvable with conditions. One of those conditions would be to make sure that you get the entire patient cohort but that isn't necessarily going to hold up the approvability which is what I think I'm hearing based on the motion.

DR. SWAIN: Okay. Mitchell.

DR. KRUCOFF: I would speak in support of the 12-month mortality not as an efficacy issue. I think efficacy is clearly demonstrated, but just as a safety issue if this unique mechanical intervention either technically or physiologically takes a direction that we would not anticipate.

I think a formal composite of what would to me be fascinating data for 12 months. Frankly, with this group it probably would get done but I have to say as a part of the panel from this side of the table, I feel that it is important for us and wading into a new indication for a new device that is going to get into the real world and be used in a less than pristine group such as has been presented here.

Having an awareness of what is really going on at 12 months which would be six on for half the cohort and 12 on for the other half would be very reassuring to me if it was negative. I could live with the functional data.

DR. DOMANSKI: But you're going to have the mortality stuff because they are reporting complications so if your concern is complications with the lead, you're going to have that without this mandate.

MS. PINA: I don't think -- sorry Mitch. I don't think that any of the other mortality trials are going to be coming out in the next six months. Certainly Scott Heff is not going to come out in the

next six months. I think that six months is reasonable which is what we would wait for another six months.

DR. KRUCOFF: And collecting mortality, I mean, this is not redoing functional stress tests or echos. I think collecting mortality data on this well-characterized cohort who are undergoing pacemaker surveillance and heart failure surveillance anyway would have a lot of interest just from my perspective on the panel from a safety perspective.

DR. SWAIN: You think approval of the device should be held up by the FDA?

DR. KRUCOFF: I'm not saying that. No. This is approval with conditions.

DR. SWAIN: Okay.

DR. KRUCOFF: Approval with conditions.

DR. SWAIN: I'll only make my comment. I agree with Mike.

Any other comments about this?

DR. AZIZ: It would be fairly easy to have the data. I think as Mitch was saying, I don't think it's going to delay use of the device. I think

whenever you do things in heart failure where the patient feels better.

Like we saw with inotropes, the patients felt better but they died from other problems. I don't think it's going to detract from its use but I think it's important data to have. Personally I don't think it will be very difficult to accumulate that data. In six months it will be yea or nay.

DR. DOMANSKI: But it's uninterpretable by treatment group unless -- it's uninterpretable by treatment groups. If there are lead problems, I mean, they are going to report lead problems and stuff like that. What are you going to do if there is no difference? Does that mean there is no difference in mortality? You can't say that because they have been treated for six months.

DR. AZIZ: I mean, if you did find an increased mortality.

MS. PINA: Increase from what?

DR. LASKEY: Well, what if there is a trend, Mike? I mean, it's difficult to play rigorous statistics here with this type of analysis but if

there is a trend, it should raise a flag.

DR. DOMANSKI: What will that flag do? What is the practical implication of it? You're going to make these guys -- I mean, it's kind of a principle with me. I don't think actually they have too much trouble collecting it but I think the data -- I'm not sure what anyone is going to do with that flag. Certainly not pull their device off the market. I'm not sure what the means.

DR. HAIGNEY: You know, I think that on the question of the lead, I don't think the lead performance information that we get from Medtronic would pick up some of the important failures that could occur.

Let's say the lead stops capturing at 12 months. It's not going to result in an explant of the lead necessarily. In the performance report it may not show up as a failure. It wouldn't be the same thing as if you had an insulation break or some other complication. I think it would be good to have a formal process to make sure that lead is still functioning and you still have resynchronization at 12

months.

DR. DOMANSKI: That, though, is not what her motion picks up, or at least as I understood it. Maybe it does but they wanted a mortality analysis. Maybe we could ask the company. Maybe we could ask Dr. Stanton what we would pick up with the usual surveillance as opposed to what is being asked for here.

DR. STANTON: Well, this lead would be included in our chronic lead study. Just to point out for people, we do two types of analyses in the reports. We sent out reports to all implanters in the United States twice a year for our brady and our tachy products.

There are two types of analysis. One is on return product which is just everything that is sent in and, frankly, is probably less valuable than the chronic lead study which we do in a number of centers. At those centers we would pick up the complications.

DR. HAIGNEY: But that would be at certain selected centers and may not reflect the experience.

DR. STANTON: Well, we don't choose the

centers to be what might be the best implanting centers in the nation because we want a cross-section.

MS. PINA: Maybe I'm wrong but you're not going to stop following these patients until they reach their six-months.

DR. STANTON: We're going to follow these patients until the conclusion of the study. We have a number of patients who are at 12 months and beyond now. There are 12-month data that we will in the final report show to the FDA. The data are there.

What I completely agree with Dr. Domanski and others on is that doing continued study of all the patients until they all reach 12 months is not going to provide you with meaningful data.

Interesting data, yes, but I'm not sure it would be meaningful in that you would be able to make a decision one way or the other based on whether the curves have separated one way, gone together, or separated the other way because you have no comparator.

I understand that, but I think we are putting little pieces of the puzzle as we try to fit

all these therapies into where they should go. The more we learn, the more we know about what to do with the patients.

I think there is very much of a clinical relevance here. We have been learning about certain drugs by, again, putting pieces of the puzzle. If you are already collecting that anyway, you have some patients already at 12 months, you have another 40 or 30 in each group that you need to bring to the six months, I'm wondering how difficult it is to just follow them out an additional six months.

DR. SWAIN: Jim

MR. DILLARD: Jim Dillard. Maybe I'll make a comment. Let me give you a regulatory perspective which is increasingly difficult for us in the current environment to go back to the manufacturer and say it would be really nice to have this data because everybody is going to want to look at it and not have a real focused issue or question that we know a priori that we are trying to answer by getting some amount of data.

I mean, I say that not because I don't think

intellectually this information isn't going to be helpful, useful, or interesting. I think from a regulatory perspective if you put me in the position of just giving me that recommendation and not what to focus on in terms of the issue that is important or derived from the clinical study, it's going to be more and more difficult for me to go back and say to Medtronic that I have to have this because I don't have the "because" to follow that.

DR. SWAIN: I think you've got the spirit of the discussion.

MR. DILLARD: I do.

DR. SWAIN: We'll the advisory panel, we'll vote, and it will be your decision.

Are there any other -- besides these four conditions that we're going to be voting on individually, any other conditions anybody has?

MS. PINA: Julia, have we discussed the labeling of the patient inclusion? Maybe I left that out of the motion.

DR. SWAIN: It's modified labeling like we've discussed. It's in the minutes.

Okay. We should now vote on each condition.

MR. DILLARD: Yes. Please do it that way. Then you can vote on the whole motion.

DR. SWAIN: Okay. So the first condition is that the data for the six-month data be acquired eventually by the FDA. Is that correct? We've had a motion made. Have you seconded all the conditions?

DR. KRUCOFF: Yes.

DR. SWAIN: Okay. Yes. All in favor of acquiring the remainder of the six-month data, put your hands up.

MS. MOYNAHAN: Seven. I guess that unanimous for this group.

DR. SWAIN: Okay. Then there is no one opposed. Okay. That passes. The second is that the echo data be completed for the database. Any other comments about that? Okay. All in favor of that?

MS. MOYNAHAN: Six. Dr. Laskey?

DR. LASKEY: I'm still sitting over here struggling. To me it's easier to do a head count at a year than to get people in to do doppler echo for an hour. To me it doesn't add up.

DR. SWAIN: Okay. So I assume that means no on that motion. So you've got that recorded. The question of acquiring the 12-month mortality data in an intent to treat. How many in favor of that?

MS. MOYNAHAN: Five.

DR. SWAIN: And how many against that?

MS. MOYNAHAN: Dr. Domanski and Dr. Kaptchuk.

DR. SWAIN: Okay. And Dr. Wittes has left so she is not voting. The modified labeling such as all of these suggestions we've all made. How many in favor of that?

MS. MOYNAHAN: Seven.

DR. SWAIN: And against? None, I believe. Okay. The final motion will be to approve with the conditions that have been accepted. That is a motion that you have made and you've seconded it. Do you have a comment?

DR. DOMANSKI: No, no.

DR. SWAIN: Okay. In favor of that approval with conditions?

MS. MOYNAHAN: Seven.

DR. SWAIN: And against? No one left. I think that finishes it. Thank you all for coming.

MS. MOYNAHAN: Can we get a poll?

DR. SWAIN: Excuse me.

MS. MOYNAHAN: Just have each panel member summarize their vote and the reason for it.

DR. SWAIN: Oh, I'm sorry. Sit down. Okay. Mike, summarize. Any other additional comments?

DR. DOMANSKI: No. I think they have demonstrated safety and effectiveness.

DR. SWAIN: Dr. Laskey.

DR. LASKEY: I echo that.

MS. PINA: I made the motion.

DR. SWAIN: Okay.

DR. HAIGNEY: I agree.

DR. KRUCOFF: I agree.

DR. AZIZ: I agree.

DR. SWAIN: Okay.

MS. MOYNAHAN: Open public hearing.

DR. SWAIN: Wait a minute. One more little open public hearing. Open public hearing. Are there any comments from the public? Thank you. The public

meeting is closed and the meeting is adjourned. Thank you.

(Whereupon, at 4:55 p.m. the hearing was adjourned.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Circulatory System Devices Panel of the Medical Devices Advisory Committee

Before: DHHS/FDA/CDRH

Date: July 10, 2001

Place: Gaithersburg, MD

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.